REMARKS

The Office Action of September 22, 2005 has been received and reviewed.

Claims 1-12 and 19 are currently pending in the application.

Claims 1-6, 9-12 and 19 stand rejected.

Claims 7 and 8 are allowed.

Claim 9 has been amended to address a typographical inconsistency: the word "of" was missing.

Claim 19 has been amended as suggested by the Examiner to overcome the rejection under 35 U.S.C. § 112, first paragraph.

All cancellations and amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested. Furthermore, Applicants again request the Examiner to record or note the change of address regarding the Power of Attorney for this application (see also the original Revocation of Power of Attorney of October 7, 2002, copy attached to Amendment of June 28, 2005).

Rejections Under 35 U.S.C. § 102(e)

Anticipation based on U.S. Patent No. 5,928,914 to Leboulch et al.

Claims 9 and 10 stand rejected under 35 U.S.C. § 102(e) as assertedly being anticipated by U.S. Patent No. 5,928,914 to Leboulch et al. (hereinafter referred to as "Leboulch et al."). (*See*, Office Action of September 22, 2005, at page 3, hereinafter referred to as "Office Action"). Applicants traverse the rejection as set forth herein.

Specifically, it was thought that Leboulch et al. disclose a vector comprising two *loxP* sites that cannot be recombined. However, Leboulch et al. do not disclose each and every element of claim 9. Claim 9 recites, in part, that the mutant *loxP* sequence comprises a sequence of which a part of said inverted repeat sequence 1 of *loxP* is mutated, emphasis added.

In contrast, Leboulch et al. do not disclose mutations within the *inverted repeat* sequences of the *loxP* site. The invention disclosed by Leboulch et al. is based on a mutation found in the spacer region between the two inverted repeats, not a mutation within the inverted repeats themselves. (*See*, Leboulch et al., for instance, at column 5, lines 43-51, wherein it is stated that "the other incompatible lox sequence can be a mutated form of the LoxP1 sequence, for example, having a point mutation *in the eight nucleotide spacer sequence*," emphasis added, and further at lines 18-25, wherein it is stated that incompatibility can be achieved by preferably mutating "one of two identical lox sequences, preferably in their spacer sequences," also see, for instance, claim 3 reciting a mutation in the spacer sequences).

Dependent claim 10 is not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 9.

Reconsideration and withdrawal of the anticipation rejection of claims 9 and 10 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Obviousness Rejections Based on U.S. Patent No. 5,928,914 to Leboulch et al. in view of Araki et al.

Claims 1-6, 11 and 12 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Leboulch et al. in view of Araki et al., *Targeted integration of DNA using mutant lox sites in embryonic stem cells*, *Nuc. Acids Res.*, 1997, 25(4):868-872, hereinafter referred to as "Araki et al." (Office Action, at page 3). Applicants traverse the rejection as hereinafter set forth.

M.P.E.P. § 706.02(j) provides the standard for establishing a *prima facie* case of obviousness as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Specifically, the Examiner states that Leboulch et al. also teach that one of the two *loxP* sequences can be a *loxP1* and a mutant form of *loxP* and that Araki et al. teach site directed integration using *lox71* and *lox66* in mouse ES cells. (*Id.* at pages 3-4). Claim 1 recites a trap vector comprising a *loxP* sequence and a mutant *loxP* sequence, wherein the *loxP* sequence comprises in sequential order inverted repeat sequence 1, a spacer sequence, and inverted repeat

sequence 2, and the mutant *loxP* sequence comprises a sequence in which a part of said inverted repeat sequence 1 of *loxP* is mutated.

Regarding Leboulch et al., Applicants refer the Examiner to the prior discussion concerning the identity of the sequences recited in the claims of the present application, that is, that Leboulch et al. only disclose mutations within the spacer region, not the inverted repeat region, of *loxP*.

Furthermore, Araki et al. only teach that recombination efficiency is increased by the use of *lox71* and *lox66* together, not a single vector containing both *loxP* and *lox71* OR *lox66*. Thus, Leboulch et al. even in combination with Araki et al. do not teach all the elements as claimed in claims 1 and 4 of the present invention. Therefore, Leboulch et al. and Araki et al. are not sufficient to support a *prima facie* obviousness rejection.

Additionally, the Examiner states that Araki et al. teach that *loxP* and *lox71* or *lox66* do not recombine efficiently in mouse ES cells. (*Id.*). However, Araki et al. contains no reference or data measuring the reverse reaction that yields the starting products. Araki et al. do disclose that "(t)he targeting frequencies for normal *loxP* sites were very low." (*See*, Araki et al. at page 870). The frequencies reported by Araki et al. in Table 1 are obtained using the final amount of a product of interest. This final result or yield of product includes any reduction of the amount of the product due to a reverse reaction, yielding the initial reactants. Thus, since the targeting frequencies were "very low," the recombination efficiency of the reverse reaction, yielding the initial starting material, must be rather high. In contrast, the invention of the present application is directed to mutations in two *loxP* inverted repeat sites that, when combined with *loxP*, create

very low occurrence of the reverse reaction. Neither Araki et al. nor Leboulch et al. disclose this concept, or benefit therefrom.

Dependent claims 2, 3, 5, 6, 11 and 12 are non-obvious for similar reasons as discussed above.

Reconsideration and withdrawal of the obviousness rejection of claims 1-6, 11 and 12 are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Enablement

Claim 19 stands rejected under 35 U.S.C. § 112, first paragraph, for assertedly failing to comply with the enablement requirement. (*See*, Office Action, at page 5). Applicants traverse the rejection as set forth herein.

Specifically, the Examiner states that critical components such as SA, IRES and a marker gene are required for the practice of the gene trapping method and that the disclosure does not enable a gene trapping method using vectors that comprise only *loxP* sites. (*Id.*). However, claim 7 has been allowed and recites a trap vector comprising only a marker gene. (*See*, claim 7(e)). Thus, claims directed to a trap vector comprising a marker gene, as in claim 7, must be enabled. Therefore, amended claim 19 is directed to a method of gene trapping, comprising introducing into an embryonic stem cell a trap vector comprising a *loxP* sequence, a marker gene and a mutant *loxP* sequence. Claim 19, as amended, now recites the element "a marker gene," as suggested by the Examiner, and is now believed to be fully enabled by the disclosure. (*See*, Office Action, at page 5, wherein it is stated, "critical components such as SA, IRES and marker

is required for the practice of the 'gene trapping method.'"). Support for this amendment can be found, for instance, in the as-filed specification at page 14 and in the original claims, such as claim 7.

New claim 20 has been added and is dependent from claim 19. Support for new claim 20 may be found in the as-filed specification, for instance, at page 14 and original claim 7.

Reconsideration and withdrawal of the enablement rejection of claim 19 is respectfully requested.

ENTRY OF AMENDMENTS

The proposed amendments to claim 9 and 19 and new claim 20 should be entered by the Examiner because the amendments are supported by the as-filed specification and do not add any new matter to the application. The proposed amendments and new claim 20 should also be entered since they comply with the requirements as to form, *i.e.*, they remove 35 U.S.C. § 112, first paragraph rejections. Furthermore, the amendments and new claim 20 do not raise new issues or require a further search since the amendments incorporate elements from other claims already presented. Finally, if the Examiner determines that the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the claims define patentable subject matter and a notice of allowance is requested. If any questions remain after consideration of the foregoing, the Office is invited to contact the Applicants' attorney at the address or telephone number given herein.

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Respectfully submitted,

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